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Is Smoking Still Important in the Pathogenesis of Peptic Ulcer Disease?

Gregory L. Eastwood, M.D.

The pathogenesis of peptic ulcer disease is multifactorial, including the effects of *Helicobacter pylori*, gastric acid, pepsin, gastroduodenal motility, smoking and nicotine, and the complex interaction of an array of other so-called aggressive and protective factors. Since the discovery and acceptance of *H. pylori* as a major etiologic agent in peptic ulcer disease, the role of smoking has received less attention. Smokers are more likely to develop ulcers, ulcers in smokers are more difficult to heal, and ulcer relapse is more likely in smokers. These clinical observations may be explained by the adverse effects that smoking has on mucosal aggressive and protective factors. Of the aggressive factors, smoking appears to have no consistent effect on acid secretion. However, smoking impairs the therapeutic effects of histamine-2 antagonists, may stimulate pepsin secretion, promotes reflux of duodenal contents into the stomach, increases the risk for and harmful effects of *H. pylori*, and increases production of free radicals, vasopressin, secretion by the pituitary, secretion of endothelin by the gastric mucosa, and production of platelet activating factor. Smoking also affects the mucosal protective mechanisms. It decreases gastric mucosal blood flow and inhibits gastric mucous secretion, gastric prostaglandin generation, salivary epidermal growth factor secretion, duodenal mucosal bicarbonate secretion, and pancreatic bicarbonate secretion. These adverse effects of smoking on aggressive and protective factors quality it as an important contributor to the pathogenesis of peptic ulcer disease and indicate that smoking plays a significant facilitative role in the development and maintenance of peptic ulcer disease.

Key Words: Smoking—Peptic ulcer disease—*Helicobacter pylori*—mucosal injury and protection.

The pathogenesis of peptic ulcer disease is multifactorial, including the effects of *Helicobacter pylori*, gastric acid, pepsin, gastroduodenal motility, smoking and nicotine, and the complex interaction of an array of other so-called aggressive and protective factors. Since the discovery and acceptance of *H. pylori* as a major etiologic agent of peptic ulcer disease, the role of smoking has received less attention. This review should remind us that smoking still is an important factor in the pathogenesis of peptic ulcer disease because it adversely affects many of the natural protective mechanisms and enhances the aggressive ones, including increasing the risk for *H. pylori* infection.

Historically, smoking has been viewed as both a benign pleasure and a dangerous habit. More than 300 years ago, Moliere (1622–1673) said, ". . . there's nothing like tobacco. 'Tis the passion of decent folk; and he who lives without tobacco isn't worthy of living."

A century later, Philip Freneau (1752–1832) offered a more critical view:

> Tobacco surely was designed
> To poison, and destroy mankind.

More recently, this verse by Graham Lee Hemminger (1896–1949) expresses our contemporary ambivalence toward smoking.

> Tobacco is a dirty weed. I like it.
> It satisfies no normal need. I like it.
> It makes you thin, it makes you lean,
> It takes the hair right off your bean.
> It's the worse darn stuff I've ever seen.
> I like it.

Regardless of what people historically have thought about smoking, the fact remains that smoking and nicotine do have adverse effects that contribute to the pathogenesis of peptic ulcer disease.

What is the evidence that smoking and peptic ulcer disease are causally linked? (Table 1). First, ciga-

From the State University of New York Health Science Center and Syracuse, Syracuse, New York.

Address correspondence and reprint requests to Dr. G. L. Eastwood at the SUNY Health Science Center at Syracuse, 750 E. Adams St., Syracuse, NY 13210-2399 U.S.A.

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TABLE 1. *Clinical associations of smoking with peptic ulcer disease*

Smokers are more likely than non-smokers to develop ulcers
Ulcers in smokers are more difficult to heal
Ulcer relapse is more likely in smokers

rette smoking appears to be a risk factor for the development, maintenance, and recurrence of peptic ulcer disease. Epidemiologic evidence indicates that (a) smokers are more likely to develop peptic ulcers than nonsmokers (1–5), (b) once formed, peptic ulcers in smokers are more difficult to heal (2,6–10), and (c) after ulcers have healed, they are likely to relapse sooner and more often in smokers than in nonsmokers (8,11,12). These clinical observations might be explained by the effects of smoking and nicotine on various physiologic functions of the upper gastrointestinal tract, some of which can injure and others that can protect the mucosa.

INJURIOUS (AGGRESSIVE) FACTORS

Gastric Acid Secretion and Histamine-2 Antagonists

The medical literature tells a variable and sometimes contradictory story about the effect of smoking on gastric acid secretion. Smoking has been reported to either stimulate (13–16), inhibit (17–19), or have no effect on acid secretion (20–22). In one study, a biphasic effect, i.e., an initial transient rise in basal acid secretion followed by a decrease, was seen after smoking one unfiltered cigarette every 15 min for 1 h (23). In another study, smokers with duodenal ulcer who smoked four cigarettes did not have a change in basal gastric acid secretion, but habitual heavy smokers who were not actively smoking at the time of study did exhibit an increase in pentagastric-stimulated gastric secretion compared to nonsmokers (14).

With respect to histamine-2 (H_2) antagonists, smoking appears to interfere with the antisecretory actions of cimetidine, ranitidine, and famotidine. For example, nocturnal acid secretion was greater in smokers treated with H_2 antagonists when they were allowed to smoke than when smoking was prohibited (24). In another trial, three H_2 antagonist regimens (cimetidine 800 mg h.s., ranitidine 150 mg b.i.d., and ranitidine 300 mg h.s.) were all less effective in smokers than in nonsmokers in reducing gastric acidity (25). In addition, smokers with duodenal ulcers treated with H_2 antagonists have poorer rates of healing (8,9). This means that H_2 antagonists appear to be less effective in healing duodenal ulcers in smokers, although increasing the dosage may overcome this problem (9). Moreover, treatment with sucralfate may be more effective than H_2 antagonists in healing duodenal ulcers and preventing relapse in smokers (26). In gastric ulcers treated with H_2 antagonists, smoking does not appear to affect adversely the healing or recurrence rate (27–29). To summarize, although it is likely that smoking has no consistent, clinically important effect on gastric acid secretion, smoking does appear to interfere with the effectiveness of H_2 antagonists in healing duodenal ulcers.

Pepsin Secretion

The activity of pepsin is dependent on pH. Therefore, the role of pepsin in the pathogenesis of peptic ulcer disease is linked to acid. In one study, basal, vagally stimulated, and maximal outputs of pepsin were significantly higher in smokers than in nonsmokers, whether or not they had duodenal ulcer (16). In another study, smokers with ulcers had significantly greater pepsin secretion after pentagastrin or histamine stimulation than nonsmokers with ulcers, but in subjects without ulcers there was no significant association between smoking and stimulated pepsin secretion (30). These observations suggest that smoking either stimulates or does not affect pepsin secretion.

Upper Gastrointestinal Motility

Changes in gastric emptying and reflux of duodenal contents into the stomach may contribute to gastric mucosal injury. Data on the effects of smoking on gastric emptying are conflicting. Various studies show that smoking increases, delays, or does not affect gastric emptying of solids or liquids (31–36). In contrast to information on gastric emptying, there is ample evidence to implicate smoking in promoting duodenogastric reflux. Smoking a single cigarette relaxes the pyloric sphincter (37). Other studies show that smoking is associated with reflux of duodenal contents into the stomach (21,38–40), although this has not been universally documented (41). Therefore, although the effects of smoking on gastric emptying are not clear, smoking does appear to promote reflux of duodenal contents, including bile acids, phospholipids, and pancreatic secretions, into the stomach, where they can promote gastric mucosal injury.

H. pylori

The identification of *H. pylori* and its primary role in the pathogenesis of peptic ulcer disease undoubt-

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edly is one of the most significant medical discoveries of this century. What, therefore, is the relationship of *H. pylori* to smoking in the pathogenesis of peptic disease and its treatment?

First, smoking appears to increase the risk for *H. pylori* infection in individuals without peptic ulcer disease. In one study of 462 subjects with normal endoscopy, current cigarette smokers had a higher rate of *H. pylori* infection (50%) than nonsmokers and ex-smokers (36%) (42).

Second, this effect of smoking on increasing the likelihood of *H. pylori* infection is magnified in African-Americans. African-Americans are more likely than whites to have *H. pylori* infection (43–45), and that risk is increased almost 10-fold in African-Americans who smoke (45).

Third, smoking may enhance the formation of ulceration in *H. pylori*-positive individuals. In one study, 73% of *H. pylori*-seropositive smokers had a duodenal or gastric ulcer, whereas only 27% of seropositive nonsmokers had ulcers (46). However, another study failed to identify an additional risk of smoking for ulceration that was independent of *H. pylori* infection (47).

Fourth, in support of the contention that smoking enhances the ulcerogenic actions of *H. pylori*, nicotine has been shown to potentiate the effect of a vacuolating toxin produced by *H. pylori* (48). About 50% of *H. pylori* isolates produce a vacuolating toxin, which may be an important determinant of virulence and can be detected in vitro by quantifying vacuolation of HeLa cells. Nicotine alone induces vacuolization, but when added to *H. pylori* it potentiates the vacuolating effect of the *H. pylori* toxin (48).

Fifth, cigarette smoking appears to have no effect on ulcer healing after eradication of *H. pylori* (49).

Finally, eradication of *H. pylori* appears to obviate the deleterious effect of smoking on subsequent relapse of ulcer. Two studies have shown that when *H. pylori* is treated effectively, whether a patient smokes or not has no effect on the risk for recurrence (50,51).

To summarize, smoking appears to increase the risk for *H. pylori* infection, which may be more pronounced in African-Americans, and may also augment the harmful effects of *H. pylori* in the development of peptic ulceration. However, once *H. pylori* has been eradicated, smoking does not appear to delay ulcer healing or increase the risk for recurrence.

Other Aggressive Factors

Smoking also affects several other aggressive factors in ways that may promote mucosal injury.

Oxygen-derived free radicals are important in the pathogenesis of gastric mucosal injury by ethanol, nonsteroidal anti-inflammatory drugs, restraint stress, and other provocative agents and conditions (52–54). In one study, production of white cells and blood free radicals was increased in smokers compared to nonsmokers, suggesting that free radicals promote gastric mucosal injury in smokers (54).

Agents that cause vasoconstriction may predispose to mucosal injury. Several reports have shown that both smoking and i.v. nicotine stimulate the pituitary to release vasopressin, a potent vasoconstrictor (55–58). In addition, the endothelin peptides, which are vasoconstrictors produced by endothelial cells, have been implicated in various forms of gastric mucosal damage (59–61). In dogs, cigarette smoke has been shown to increase gastric mucosal endothelin peptide (ET-1) content (62). Finally, platelet-activating factor (PAF) is an endogenous phospholipid that has vasoconstrictive properties and has been identified as a mediator of gastric mucosal injury under several conditions (63–65). Plasma PAF concentrations are elevated in smokers (66), which may be due to inhibition of plasma PAF acetylhydrolase activity by cigarette smoke (67).

PROTECTIVE FACTORS

Mucus Secretion

In rats, intragastric nicotine initially stimulates mucus secretion (68–71), but chronic administration depresses mucus secretion, gastric mucosal mucus content, and total mucus neck cell population (68,71, 72). In humans, smokers had a reduction in acid mucosubstances in gastric epithelium compared to nonsmokers (73). Therefore, the long-term effect of smoking appears to be inhibition of gastric mucus.

Prostaglandin Generation

Prostaglandins, particularly of the E and I series, are believed to be important in protecting the gastroduodenal mucosa against injury. Some of the beneficial effects of prostaglandins include stabilization of mucosal capillary endothelial integrity, maintenance of mucosal blood flow, and stimulation of mucus and bicarbonate from mucosal surface epithelial cells.

Several studies have shown that smoking in humans causes immediate but transient reductions in both luminal and gastric mucosal PGE_2 and 6-keto-PGF_{1a} (74–77), the so-called protective prostaglandins, and increases in luminal PGF_{2a} and thromboxane B_2 (78), prostaglandins that are more harm-

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ful. Whether these observations are due to the luminal effects of nicotine on the gastric mucosa or to some systemic effect has been addressed by the following studies. In rats, an ulcerogenic i.v. dose of nicotine (79), intragastric instillation of nicotine in various concentrations (80), and incubation of mucosal samples in vitro with a wide range of concentrations of nicotine (81) all failed to alter gastric mucosal PGE_2 and 6-keto-PGF_{1a} generation. Therefore, although smoking appears to depress gastric mucosal prostaglandin generation, the mechanism is not likely to be via a direct effect of nicotine.

Mucosal Blood Flow

With regard to mucosal blood flow, the effects of nicotine and smoking are equivocal, i.e., nicotine administration or smoking in animals and humans has been shown to increase, decrease, have no effect, or have variable effects on mucosal blood flow (82–86). Part of the problem is the variety of methods for measuring mucosal blood flow, which include measurement of Neutral Red clearance, aminopyrine clearance, hydrogen gas clearance, and Doppler flowmetry. However, on balance, it appears that nicotine and smoking decrease gastric mucosal blood flow by a variety of effects, including a systemic reduction in arterial blood pressure and an increase in intestinal vascular resistance. The latter could be mediated by a variety of factors, including activation of adrenoreceptors, and some of the effects already discussed, i.e., stimulation of vasopressin secretion by smoking, generation of platelet-activating factor and endothelin, and inhibition of endogenous prostaglandin synthesis.

Epidermal Growth Factor

Epidermal growth factor (EGF) is a mucosal protective agent that is secreted in saliva and swallowed into the stomach, where it binds to receptors in the gastric mucosa to inhibit gastric acid secretion (87). Several reports indicate that smoking cigarettes is accompanied by a reduction in salivary secretion of EGF (88,89). Reduced EGF in smokers may contribute to an increased risk for peptic ulcer disease by increasing acid secretion and diminishing mucosal protection.

Pancreatic and Duodenal Mucosal Bicarbonate Secretion

Both pancreatic bicarbonate secretion and duodenal mucosal bicarbonate secretion are important in neutralizing gastric acid as it enters the proximal duodenum and thereby helping to protect the duodenal mucosa from the harmful effects of acid and pepsin. Several studies have shown that, immediately after smoking, pancreatic secretion of bicarbonate is diminished and the pH of the duodenal bulb becomes more acid (23,90–92). These effects are transient, lasting minutes to hours. Smoking also has been shown to inhibit acid-stimulated duodenal mucosal bicarbonate secretion, although there was no effect on luminal PGE_2 (93). The inhibition by smoking of both pancreatic and duodenal mucosal bicarbonate secretion, and the consequent compromise in neutralizing acid, may predispose to peptic disease of the duodenum.

OVERVIEW AND COMMENT

Clinical and epidemiologic evidence indicates that smokers are more likely to develop ulcers, ulcers in smokers are more difficult to heal, and ulcer relapse is more likely in smokers (Table 1). These clinical observations may be explained by the adverse effects of smoking on mucosal aggressive and protective factors, factors that are believed to be important in the development and avoidance of mucosal injury.

With regard to the aggressive factors (Table 2), although smoking appears to have no consistent clinically important effect on gastric acid secretion, it does impair the therapeutic effects of H_2 antagonists. Smoking also appears to stimulate pepsin secretion. Although the effects of smoking on gastric emptying are not consistent, smoking does cause relaxation of the pyloric sphincter and promotes reflux of duodenal contents into the stomach. The interaction of smoking with *H. pylori* is of particular relevance in view of the causative role played by *H. pylori* in the pathogenesis of peptic ulcer disease. Smoking appears to increase the risk for *H. pylori* infection, which may be more pronounced in African-Americans, and may also augment the harmful effects of *H. pylori* in the development of peptic ulceration. However, once *H. pylori* has been eradicated, smoking does not appear to delay ulcer healing or increase the risk for recurrence. Smoking

TABLE 2. *Effects of smoking on aggressive factors*

No consistent effect on acid secretion
Impairs the effects of histamine-2 antagonists
May stimulate pepsin secretion
Promotes reflux of duodenal contents
Increases risk for *H. pylori* infection and potentiates its harmful effects
Increases free radical production, pituitary vasopressin, gastric mucosal endothelin, and platelet-activating factor

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TABLE 3. *Effects of smoking on protective factors*

Inhibits gastric mucus secretion
Inhibits gastric mucosal prostaglandin generation
Decreases mucosal blood flow
Inhibits salivary epidermal growth factor secretion
Inhibits pancreatic bicarbonate secretion
Inhibits duodenal mucosal bicarbonate secretion

affects several other aggressive factors, including increases in free radical production, pituitary vasopressin, gastric mucosal ET-1 and PAF.

Smoking also affects mucosal protective mechanisms (Table 3). It inhibits mucous secretion as well as mucosal prostaglandin generation. Smoking also decreases mucosal blood flow, which may be mediated by a variety of factors, including activation of adrenoreceptors and stimulation of vasopressin secretion, generation of PAF and ET-1, and inhibition of endogenous prostaglandin synthesis. Finally, smoking inhibits salivary EGF secretion, duodenal mucosal bicarbonate secretion, and pancreatic bicarbonate secretion, all of which are important in protection of the gastric and duodenal mucosa.

The adverse effects of smoking on aggressive and protective factors qualify it as an important contributor to the development and maintenance of peptic ulcer disease. However, these effects are transient and the affected physiologic functions return to normal within minutes to hours after cessation of smoking. In contrast to the effects of smoking on coronary artery disease, stroke, chronic lung disease, cancer, and complications of pregnancy, which are either permanent or can persist for years after cessation of smoking, cessation of smoking appears to have immediate beneficial effects on peptic ulcer disease.

REFERENCES

1. Friedman GD, Siegelaub AB, Seltzer CC. Cigarettes, alcohol, coffee and peptic ulcer. *N Engl J Med* 1974;290:469–73.
2. Harrison AR, Elashoff JD, Grossman MI. Cigarette smoking and ulcer disease. In: *Smoking and health: a report of the Surgeon General.* Washington, DC: US Department of Health, Education, and Welfare, Government Printing Office, 1979:9.3–9.21.
3. Ainley CC, Forgacs IC, Keeling PW, Thompson RP. Outpatient endoscopic survey of smoking and peptic ulcer. *Gut* 1986;27:648–51.
4. Stemmermann GN, Marcus EB, Buist AS, MacLean CJ. Relative impact of smoking and reduced pulmonary function on peptic ulcer risk. A prospective study of Japanese men in Hawaii. *Gastroenterology* 1989;96:1419–24.
5. Anda RF, Williamson DF, Escobedo LG, Remington PL. Smoking and the risk of peptic ulcer disease among women in the United States. *Arch Intern Med* 1990;150:1437–41.
6. Doll R, Jones FA, Pygott F. Effect of smoking on the production and maintenance of gastric and duodenal ulcers. *Lancet* 1958;1:657–62.
7. Herrmann RP, Piper DW. Factors influencing the healing rate of chronic gastric ulcer. *Am J Dig Dis* 1973;18:1–6.
8. Korman MG, Hansky J, Eaves ER, Schmidt GT. Influence of cigarette smoking on healing and relapse in duodenal ulcer disease. *Gastroenterology* 1983;85:871–4.
9. Ireland A, Colin-Jones DG, Gear P, et al. Ranitidine 150 mg twice daily vs 300 mg nightly in treatment of duodenal ulcers. *Lancet* 1984;2:274–6.
10. Kato I, Nomura AMY, Stemmermann GN, Chyou P-H. A prospective study of gastric and duodenal ulcer and its relation to smoking, alcohol, and diet. *Am J Epidemiol* 1992;135:521–30.
11. Ippoliti A, Elashoff J, Valenzuela J, et al. Recurrent ulcer after successful treatment with cimetidine or antacid. *Gastroenterology* 1983;85:875–80.
12. Sontag S, Graham D, Belsito A, et al. Cimetidine, cigarette smoking, and recurrence of duodenal ulcer. *N Engl J Med* 1984;311:689–93.
13. Piper DW, Raine JM. Effect of smoking on gastric secretion. *Lancet* 1959;1:696–8.
14. Parente F, Lazzaroni M, Sangaletti O, Baroni S, Porro GB. Cigarette smoking, gastric acid secretion, and serum pepsinogen I concentrations in duodenal ulcer patients. *Gut* 1985;26:1327–32.
15. Whitfield PF, Hobsley M. Comparison of maximal gastric secretion in smokers and non-smokers with and without duodenal ulcer. *Gut* 1987;28:557–60.
16. Lanas A, Hirschowitz BI. Influence of smoking on basal and on vagally and maximally stimulated gastric acid and pepsin secretion. *Scand J Gastroenterol* 1992;27:208–12.
17. Wilkinson AR, Johnston D. Inhibitory effect of cigarette smoking on gastric secretion stimulated by pentagastrin in man. *Lancet* 1971;2:628–32.
18. Sonnenberg A, Husmert N. Effect of nicotine on gastric mucosal blood flow and acid secretion. *Gut* 1982;23:532–5.
19. Roxburgh JC, Whitfield PF, Hobsley M. Effect of acute cigarette smoking on gastric secretion. *Gut* 1992;53:1170–3.
20. Debas HT, Cohen MM. Effect of smoking on gastric secretion stimulated by pentagastrin. *Lancet* 1972;1:43–4.
21. Whitecross DP, Clarke AD, Piper DW. The effect of cigarette smoking on human gastric secretion. *Scand J Gastroenterol* 1974;9:399–403.
22. Demol P, Singer MV, Hotz J, Dipp M, Goebell H. Interdigestive gastrointestinal motility and secretion of gastric acid and pancreatic enzymes in young cigarette smokers. *Digestion* 1984;29:107–11.
23. Murthy SNS, Dinoso VP, Clearfield HR, Chey WY. Simultaneous measurement of basal pancreatic, gastric acid secretion, plasma gastrin, and secretin during smoking. *Gastroenterology* 1977;73:758–61.
24. Boyd EJS, Wilson JA, Wormsley KG. Smoking impairs therapeutic gastric inhibition. *Lancet* 1983;1:95–7.
25. Bauerfeind P, Cilluffo T, Fimmel CJ, et al. Does smoking interfere with the effect of histamine H_2-receptor antagonists on intragastric acidity in man? *Gut* 1987;28:549–56.
26. Lam SK, Hui WM, Lau WY, et al. Sucralfate overcomes adverse effect of cigarette smoking on duodenal ulcer healing and prolongs subsequent remission. *Gastroenterology* 1987;92:1193–201.
27. Lyon DT. Efficacy and safety of famotidine in the management of benign gastric ulcers. *Am J Med* 1986;81(suppl 4B):33–41.
28. Naccaratto R, Cremer M, Dammann HG, et al. Nizatidine versus ranitidine in gastric ulcer disease: a European multicentre trial. *Scand J Gastroenterol* 1987;22(suppl 136):71–8.
29. McCullough AJ, Graham DY, Knuff TE, et al. Suppression of nocturnal acid secretion with famotidine accelerates gastric ulcer healing. *Gastroenterology* 1989;97:860–6.
30. Walker V, Taylor WH. Cigarette smoking, chronic peptic ulceration, and pepsin 1 secretion. *Gut* 1979;20:971–6.

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31. Grimes DS, Goddard J. Effect of cigarette smoking on gastric emptying. *BMJ* 1978;2:460–1.
32. Petring OU, Adelhoj B, Ibsen M, Brynnum J, Poulsen HE. Abstaining from cigarette smoking has no major effect on gastric emptying in habitual smokers. *Br J Anaesthesiol* 1985; 57:1104–6.
33. Hanson M, Lilja B. Gastric emptying in smokers. *Scand J Gastroenterol* 1987;22:1102–4.
34. Miller G, Palmer KR, Smith B, Ferrington C, Merrick MV. Smoking delays gastric emptying of solids. *Gut* 1989;30:50–3.
35. Johnson RD, Horowitz M, Maddox AF, Wishart JM, Shearman DJC. Cigarette smoking and rate of gastric emptying: effect on alcohol absorption. *BMJ* 1991;302:20–3.
36. Scott AM, Kellow JE, Shuter B, Nolan JM, Hoschi R, Jones MP. Effects of cigarette smoking on solid and liquid intragastric distribution and gastric emptying. *Gastroenterology* 1993; 104:410–6.
37. Valenzuela JE, Defilippi C, Csendes A. Manometric studies on the human pyloric sphincter. Effect of cigarette smoking, metoclopramide, and atropine. *Gastroenterology* 1976;70: 481–3.
38. Dippy JE, Rhodes J, Cross S. Bile reflux in gastric ulcer. The effect of smoking, metoclopramide, and carbenoxolone sodium. *Curr Med Res Opin* 1973;1:569–75.
39. Read NW, Grech P. Effect of cigarette smoking on competence of the pylorus: preliminary study. *BMJ* 1973;3:313–6.
40. Muller-Lissner SA. Bile reflux is increased in cigarette smokers. *Gastroenterology* 1986;90:1205–9.
41. Yeomans ND, Williams DR, Mackinnon MA, McLeish AR, Smallwood RA. Effect of cigarette smoking on duodenogastric reflux of bile acids. *Aust NZ J Med* 1981;11:347–50.
42. Bateson MC. Cigarette smoking and *Helicobacter pylori* infection. *Postgrad Med J* 1993;69:41–4.
43. Malaty HM, Evans DG, Evans DJ Jr, Graham DY. *Helicobacter pylori* in Hispanics: comparison with blacks and whites of similar age and socioeconomic class. *Gastroenterology* 1992;103:813–6.
44. Malaty HM, Graham DY. Importance of childhood socioeconomic status on the current prevalence of *Helicobacter pylori* infection. *Gut* 1994;35:742–5.
45. Fontham ETH, Ruiz B, Perez A, Hunter F, Correa P. Determinants of *Helicobacter pylori* infection and chronic gastritis. *Am J Gastroenterol* 1995;90:1094–101.
46. Martin DF, Montgomery E, Dobek AS, Patrissi GA, Peura DA. *Campylobacter pylori*, NSAIDS, and smoking: risk factors for peptic ulcer disease. *Am J Gastroenterol* 1989;84: 1268–72.
47. Schubert TT, Bologna SD, Nensey Y, Schubert AB, Mascha EJ, Ma CK. Ulcer risk factors: interactions between *Helicobacter pylori* infection, nonsteroidal use, and age. *Am J Med* 1993;94:413–8.
48. Cover TL, Vaughan SG, Cao P, Blaser MJ. Potentiation of *Helicobacter pylori* vacuolating toxin activity by nicotine and other weak bases. *J Infect Dis* 1992;166:1073–8.
49. O'Connor HJ, Kanduru C, Bhutta AS, Meehan JM, Feeley KM, Cunnane K. Effect of *Helicobacter pylori* eradication on peptic ulcer healing. *Postgrad Med J* 1995;71:90–3.
50. Marshall BJ, Goodwin CS, Warren JR, et al. Prospective double-blind trial of duodenal ulcer relapse after eradication of *Campylobacter pylori*. *Lancet* 1988;2:1437–42.
51. Borody TJ, George LL, Brandl S, Andrews P, Jankiewicz E, Ostapowicz N. Smoking does not contribute to duodenal ulcer relapse after *Helicobacter pylori* eradication. *Am J Gastroenterol* 1992;87:1390–3.
52. Smith SM, Kvietys PR. Gastric ulcers: role of oxygen radicals. *Crit Care Med* 1988;16:892–8.
53. Hirota M, Inoue M, Ando Y, Morino Y. Inhibition of stress-induced gastric mucosal injury by a long acting superoxide dismutase that circulates bound to albumin. *Arch Biochem Biophys* 1990;280:269–73.
54. Kalra J, Chaudhary AK, Prasad K. Increased production of oxygen free radicals in cigarette smokers. *Int J Exp Pathol* 1991;72:1–7.
55. Husain MK, Frantz AG, Ciarochi F, Robinson AG. Nicotine-stimulated release of neurophysin and vasopressin in humans. *J Clin Endocrinol Metab* 1975;41:1113–7.
56. Rowe JW, Kilgore A, Robertson GL. Evidence in man that cigarette smoking induces vasopressin release via an airway-specific mechanism. *J Clin Endocrinol Metab* 1980;51:170–2.
57. Aubert JF, Burnier M, Waeber B, Nussberger J, Brunner HR. Nicotine-induced release of vasopressin in the conscious rat: role of opioid peptides and hemodynamic effects. *J Pharmacol Exp Ther* 1987;243:681–5.
58. Laszlo F, Karacsony G, Szabo E, Lang J, Balaspiri L, Laszlo FA. The role of vasopressin in the pathogenesis of ethanol-induced gastric hemorrhagic erosions in rats. Is vasopressin an endogenous aggressor toward the gastric mucosa? *Gastroenterology* 1991;101:1242–8.
59. Whittle BJR, Esplugues JV. Induction of rat gastric damage by the endothelium-derived peptide, endothelin. *Br J Pharmacol* 1988;95:1011–3.
60. Wallace JL, Cirino G, DeNucci G, McKnight W, MacNaughton WK. Endothelin has potent ulcerogenic and vasoconstrictor actions on the stomach. *Am J Physiol* 1989;256:G661–6.
61. Morales RE, Johnson BR, Szabo S. Endothelin induces vascular and mucosal lesions, enhances the injury by HCl/ethanol, and the antibody exerts gastroprotection. *FASEB J* 1992;6:2354–60.
62. Hayashi N, Kawano S, Tsuji S, et al. Mechanisms of smoking-induced changes in gastric blood flow and mucosal oxygenation: roles of endothelin and prostacyclin [Abstract]. *Gastroenterology* 1993;104:A97.
63. Rosam A-C, Wallace JL, Whittle BJR. Potent ulcerogenic actions of platelet-activating factor on the stomach. *Nature* 1986;319:54–6.
64. Wallace JL, Steel G, Whittle BJR, Lagente V, Vargaftig B. Evidence for platelet-activating factor as a mediator of endotoxin-induced gastrointestinal damage in the rat. Effects of three platelet-activating factor antagonists. *Gastroenterology* 1987;93:765–73.
65. Wallace JL, Hogaboam CM, McKnight GW. Platelet-activating factor mediates gastric damage induced by hemorrhagic shock. *Am J Physiol* 1990;259:G140–6.
66. Imaizumi T. Intravascular release of a platelet-activating factor-like lipid (PAF-LL) induced by cigarette smoking. *Lipids* 1991;26:1269–73.
67. Miyaura S, Eguchi H, Johnson JM. Effect of a cigarette smoke extract on the metabolism of the proinflammatory autacoid, platelet-activating factor. *Circ Res* 1992;70:341–7.
68. Wong SH, Ogle CW, Cho CH. The influence of chronic or acute nicotine pretreatment on ethanol-induced gastric ulceration in the rat. *J Pharm Pharmacol* 1986;38:537–40.
69. Endoh K, Baker M, Leung FW. Mechanism of intragastric nicotine protection against ethanol-induced gastric injury. *Dig Dis Sci* 1991;36:39–46.
70. Endoh K, Kao J, Baker M, Leung FW. Involvement of alpha-2-adrenoreceptors in mechanism of intragastric nicotine protection against ethanol injury in rat stomach. *Dig Dis Sci* 1993; 38:713–21.
71. Kaunitz JD, Nishizaki Y, Kaneko K, Guth PH. Effect of orogastric nicotine on rat gastric mucosal gel thickness, surface cell viability and intracellular pH. *J Pharmacol Exp Ther* 1993;265:948–54.
72. Jarvis LR, Whitehead R. Effect of nicotine on the morphology of the rat gastric mucosa. *Gastroenterology* 1980;78:1488–94.
73. Hollanders D, Morrissey SM, Ward PM. Histochemistry of gastric mucins in smokers and non-smokers. *Br J Clin Pract* 1986;40:74–7.
74. McCready DR, Clark L, Cohen MM. Cigarette smoking reduces human gastric luminal prostaglandin E_2. *Gut* 1985;26: 1192–6.

PM3001395313

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75. Quimby GF, Bonnice CA, Burstein SH, Eastwood GL. Active smoking depresses prostaglandin synthesis in human gastric mucosa. *Ann Intern Med* 1986;104:616–9.
76. Hudson N, Daneshmend TK, Hurst S, Bhaskar NK, Brown NS, Hawkey CJ. Effect of smoking on prostaglandin, thromboxane and leukotriene synthesis by human gastric mucosa. *Adv Prostaglandin Thromboxane Leukotriene Res* 1990;21: 777–9.
77. Cryer B, Lee E, Feldman M. Factors influencing gastroduodenal mucosal prostaglandin concentrations: roles of smoking and aging. *Ann Intern Med* 1992;116:636–40.
78. Fedi P, Calabro A, Orsini B, et al. Cigarette smoking increases gastric luminal prostaglandin $F_{2\alpha}$ and thromboxane B_2 in healthy smokers. *Digestion* 1990;46:27–34.
79. Robert A. Potentiation, by nicotine, of duodenal ulcers in the rat. *Proc Soc Exp Biol Med* 1972;139:319–22.
80. Aaron JS, Bank S, Krantz V, Lendvai S. Effect of nicotine on gastric prostaglandin synthesis in the rat. [Abstract]. *Gastroenterology* 1986;90:1319.
81. Eastwood GL, Avunduk C, Quimby GF. Nicotine has no effect on rat gastric mucosal prostaglandin generation in vitro. *Dig Dis Sci* 1993;38:1450–2.
82. Gallavan RH, Tsuchiya Y, Jacobson ED. Effects of nicotine on canine intestinal blood flow and oxygen consumption. *Am J Physiol* 1984;246:G195–203.
83. Pawlik WW, Banks RO, Jacobson ED. Hemodynamic actions of nicotine on the canine stomach. *Proc Soc Exp Biol Med* 1984;177:447–54.
84. Robert ME, Leung FW, Guth PH. Nicotine and smoking do not decrease basal gastric mucosal blood flow in anesthetized rats. *Dig Dis Sci* 1986;31:530–4.
85. Cho CH, Chen BW, Hui WM, Lam SK. The influence of acute or chronic nicotine treatment on ethanol-induced gastric mucosal damage in rats. *Dig Dis Sci* 1990;35:106–12.
86. Endoh K, Kauffman GL Jr, Leung FW. Mechanism of aggravation of mucosal injury by intravenous nicotine in rat stomach. *Am J Physiol* 1991;261:G1037–42.
87. Elder JB, Ganguli PC, Gillespie IE, Gerring EL, Gregory H. Effect of urogastrone on gastric secretion and plasma gastrin levels in normal subjects. *Gut* 1975;16:887–93.
88. Konturek JW, Bielanski W, Konturek SJ, Bogdal J, Olesky J. Distribution and release of epidermal growth factor in man. *Gut* 1989;30:1194–200.
89. Jones PDE, Hudson N, Hawkey CJ. Depression of salivary epidermal growth factor by smoking. *BMJ* 1992;304:480–1.
90. Bynum TE, Solomon TE, Johnson LR, Jacobson ED. Inhibition of pancreatic secretion in man by cigarette smoking. *Gut* 1972;13:361–5.
91. Bochenek WJ, Koronczewski R. Effects of cigarette smoking on bicarbonate and volume of duodenal contents. *Am J Dig Dis* 1973;18:729–33.
92. Murthy SNS, Dinoso VP, Clearfield HR, Chey WY. Serial pH changes in the duodenal bulb during smoking. *Gastroenterology* 1978;75:1–4.
93. Ainsworth MA, Hogan DL, Koss MA, Isenberg JI. Cigarette smoking inhibits acid-stimulated duodenal mucosal bicarbonate secretion. *Ann Intern Med* 1993;119:882–6.

PM3001395314

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